

09/869/36

Welcome to STN International! Enter x:x


LOGINID:sssptal813nxx

PASSWORD:

TERMINAL (ENTER 1, 2, 3, OR ?):2

* * * * * Welcome to STN International * * * * *

NEWS 1 Web Page URLs for STN Seminar Schedule - N. America
NEWS 2 Apr 08 "Ask CAS" for self-help around the clock
NEWS 3 Apr 09 BEILSTEIN: Reload and Implementation of a New Subject Area
NEWS 4 Apr 09 ZDB will be removed from STN
NEWS 5 Apr 19 US Patent Applications available in IFICDB, IFIPAT, and IFIUDB
NEWS 6 Apr 22 Records from IP.com available in CAPLUS, HCAPLUS, and ZCAPLUS
NEWS 7 Apr 22 BIOSIS Gene Names now available in TOXCENTER
NEWS 8 Apr 22 Federal Research in Progress (FEDRIP) now available
NEWS 9 Jun 03 New e-mail delivery for search results now available
NEWS 10 Jun 10 MEDLINE Reload
NEWS 11 Jun 10 PCTFULL has been reloaded
NEWS 12 Jul 02 FOREGE no longer contains STANDARDS file segment
NEWS 13 Jul 22 USAN to be reloaded July 28, 2002;
saved answer sets no longer valid
NEWS 14 Jul 29 Enhanced polymer searching in REGISTRY
NEWS 15 Jul 30 NETFIRST to be removed from STN
NEWS 16 Aug 08 CANCERLIT reload
NEWS 17 Aug 08 PHARMAMarketLetter(PHARMAML) - new on STN
NEWS 18 Aug 08 NTIS has been reloaded and enhanced
NEWS 19 Aug 19 Aquatic Toxicity Information Retrieval (AQUIRE)
now available on STN
NEWS 20 Aug 19 IFIPAT, IFICDB, and IFIUDB have been reloaded
NEWS 21 Aug 19 The MEDLINE file segment of TOXCENTER has been reloaded
NEWS 22 Aug 26 Sequence searching in REGISTRY enhanced
NEWS 23 Sep 03 JAPIO has been reloaded and enhanced
NEWS 24 Sep 16 Experimental properties added to the REGISTRY file
NEWS 25 Sep 16 CA Section Thesaurus available in CAPLUS and CA
NEWS 26 Oct 01 CASREACT Enriched with Reactions from 1907 to 1985
NEWS 27 Oct 21 EVENTLINE has been reloaded
NEWS 28 Oct 24 BEILSTEIN adds new search fields
NEWS 29 Oct 24 Nutraceuticals International (NUTRACEUT) now available on STN
NEWS 30 Oct 25 MEDLINE SDI run of October 8, 2002
NEWS 31 Nov 18 DKILIT has been renamed APOLLIT
NEWS 32 Nov 25 More calculated properties added to REGISTRY
NEWS 33 Dec 02 TIBKAT will be removed from STN
NEWS 34 Dec 04 CSA files on STN
NEWS 35 Dec 17 PCTFULL now covers WP/PCT Applications from 1978 to date
NEWS 36 Dec 17 TOXCENTER enhanced with additional content
NEWS 37 Dec 17 Adis Clinical Trials Insight now available on STN
NEWS 38 Dec 30 ISMEC no longer available
NEWS 39 Jan 13 Indexing added to some pre-1967 records in CA/CAPLUS
NEWS 40 Jan 21 NUTRACEUT offering one free connect hour in February 2003
NEWS 41 Jan 21 PHARMAML offering one free connect hour in February 2003
NEWS 42 Jan 29 Simultaneous left and right truncation added to COMPENDEX,
ENERGY, INSPEC
NEWS 43 Feb 13 CANCERLIT is no longer being updated
NEWS 44 Feb 24 METADEX enhancements
NEWS 45 Feb 24 PCTGEN now available on STN
NEWS 46 Feb 24 TEMA now available on STN
NEWS 47 Feb 26 NTIS now allows simultaneous left and right truncation



NEWS 48 Feb 26 PCTFULL now contains images

NEWS EXPRESS January 6 CURRENT WINDOWS VERSION IS V6.01a,
CURRENT MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP),
AND CURRENT DISCOVER FILE IS DATED 01 OCTOBER 2002
NEWS HOURS STN Operating Hours Plus Help Desk Availability
NEWS INTER General Internet Information
NEWS LOGIN Welcome Banner and News Items
NEWS PHONE Direct Dial and Telecommunication Network Access to STN
NEWS WWW CAS World Wide Web Site (general information)

Enter NEWS followed by the item number or name to see news on that specific topic.

All use of STN is subject to the provisions of the STN Customer agreement. Please note that this agreement limits use to scientific research. Use for software development or design or implementation of commercial gateways or other similar uses is prohibited and may result in loss of user privileges and other penalties.

* * * * * STN Columbus * * * * *

FILE 'HOME' ENTERED AT 15:41:36 ON 03 MAR 2003

=> file biosis medline agricola embase caba wpids japio biotechds lifesci caplus
uspatall

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

FILE 'BIOSIS' ENTERED AT 15:41:51 ON 03 MAR 2003
COPYRIGHT (C) 2003 BIOLOGICAL ABSTRACTS INC.(R)

FILE 'MEDLINE' ENTERED AT 15:41:51 ON 03 MAR 2003

FILE 'AGRICOLA' ENTERED AT 15:41:51 ON 03 MAR 2003

FILE 'EMBASE' ENTERED AT 15:41:51 ON 03 MAR 2003
COPYRIGHT (C) 2003 Elsevier Science B.V. All rights reserved.

FILE 'CABA' ENTERED AT 15:41:51 ON 03 MAR 2003
COPYRIGHT (C) 2003 CAB INTERNATIONAL (CABI)

FILE 'WPIDS' ENTERED AT 15:41:51 ON 03 MAR 2003
COPYRIGHT (C) 2003 THOMSON DERWENT

FILE 'JAPIO' ENTERED AT 15:41:51 ON 03 MAR 2003
COPYRIGHT (C) 2003 Japanese Patent Office (JPO)- JAPIO

FILE 'BIOTECHDS' ENTERED AT 15:41:51 ON 03 MAR 2003
COPYRIGHT (C) 2003 THOMSON DERWENT AND INSTITUTE FOR SCIENTIFIC INFORMATION

FILE 'LIFESCI' ENTERED AT 15:41:51 ON 03 MAR 2003
COPYRIGHT (C) 2003 Cambridge Scientific Abstracts (CSA)

FILE 'CAPLUS' ENTERED AT 15:41:51 ON 03 MAR 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2003 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'USPATFULL' ENTERED AT 15:41:51 ON 03 MAR 2003
CA INDEXING COPYRIGHT (C) 2003 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'USPAT2' ENTERED AT 15:41:51 ON 03 MAR 2003
CA INDEXING COPYRIGHT (C) 2003 AMERICAN CHEMICAL SOCIETY (ACS)

=> e prof t thomas/au

E1	50	PROFT T/AU
E2	1	PROFT T L/AU
E3	35 -->	PROFT THOMAS/AU
E4	3	PROFT V/AU
E5	1	PROFT W/AU
E6	1	PROFT WILTRUD/AU
E7	1	PROFUGHI TERENCE C/AU
E8	78	PROFUMO A/AU
E9	1	PROFUMO ALBERTO/AU
E10	10	PROFUMO ALDO/AU
E11	41	PROFUMO ANTONELLA/AU
E12	79	PROFUMO E/AU

=> s e1-e3

L1 86 ("PROFT T"/AU OR "PROFT T L"/AU OR "PROFT THOMAS"/AU)

=> e fraser john d/au

E1	32	FRASER JOHN/AU
E2	1	FRASER JOHN ANGUS/AU
E3	74 -->	FRASER JOHN D/AU
E4	2	FRASER JOHN DAVID/AU
E5	11	FRASER JOHN DOUGLAS/AU
E6	2	FRASER JOHN E/AU
E7	3	FRASER JOHN F/AU
E8	6	FRASER JOHN G/AU
E9	1	FRASER JOHN J/AU
E10	4	FRASER JOHN J JR/AU
E11	1	FRASER JOHN JAMES/AU
E12	52	FRASER JOHN K/AU

=> s e3-e5

L2 87 ("FRASER JOHN D"/AU OR "FRASER JOHN DAVID"/AU OR "FRASER JOHN DOUGLAS"/AU)

=> s l1 or l12

L12 NOT FOUND

The L-number entered could not be found. To see the definition of L-numbers, enter DISPLAY HISTORY at an arrow prompt (=>).

=> s l1 or l2

L3 156 L1 OR L2

=> s l3 and superantigen

L4 66 L3 AND SUPERANTIGEN

=> s l4 and streptococc?

L5 38 L4 AND STREPTOCOCC?

=> s l5 and smez?

L6 30 L5 AND SMEZ?

=> dup rem l6

PROCESSING COMPLETED FOR L6

L7 9 DUP REM L6 (21 DUPLICATES REMOVED)

=> d bib ab 1-9

L7 ANSWER 1 OF 9 MEDLINE
AN 2003084097 IN-PROCESS
DN 22483693 PubMed ID: 12595453
TI Two novel superantigens found in both group a and group C
streptococcus.
AU **Proft Thomas**; Webb Phillip D; Handley Vanessa; **Fraser John D**
CS Department of Molecular Medicine and Pathology, Faculty of Medical and Health Sciences, University of Auckland, Auckland, New Zealand.
SO INFECTION AND IMMUNITY, (2003 Mar) 71 (3) 1361-9.
Journal code: 0246127. ISSN: 0019-9567.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS IN-PROCESS; NONINDEXED; Priority Journals
ED Entered STN: 20030222
Last Updated on STN: 20030222
AB Two novel **streptococcal superantigen** genes (speL(Se) and speM(Se)) were identified from the **Streptococcus** equi genome database at the Sanger Center. Genotyping of 8 *S. equi* isolates and 40 **Streptococcus** pyogenes isolates resulted in the detection of the orthologous genes speL and speM in a restricted number of *S. pyogenes* isolates (15 and 5%, respectively). Surprisingly, the novel **superantigen** genes could not be found in any of the analyzed *S. equi* isolates. The results suggest that both genes are located on a mobile element that enables gene transfer between individual isolates and between **streptococci** from different Lancefield groups. *S. equi* pyrogenic exotoxin L (SPE-L(Se))/**streptococcal** pyrogenic exotoxin L (SPE-L) and SPE-M(Se)/SPE-M are most closely related to **SMEZ**, SPE-C, SPE-G, and SPE-J, but build a separate branch within this group. Recombinant SPE-L (rSPE-L) and rSPE-M were highly mitogenic for human peripheral blood lymphocytes, with half-maximum responses at 1 and 10 pg/ml, respectively. The results from competitive binding experiments suggest that both proteins bind major histocompatibility complex class II at the beta-chain, but not at the alpha-chain. The most common targets for both toxins were human Vbeta1.1 expressing T cells. Seroconversion against SPE-L and SPE-M was observed in healthy blood donors, suggesting that the toxins are expressed in vivo. Interestingly, the speL gene is highly associated with *S. pyogenes* M89, a serotype that is linked to acute rheumatic fever in New Zealand.

L7 ANSWER 2 OF 9 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 1
AN 2002:513642 BIOSIS
DN PREV200200513642
TI The bacterial **superantigen streptococcal** mitogenic exotoxin Z is the major immunoactive agent of **Streptococcus** pyogenes.
AU Unnikrishnan, Meera; Altmann, Daniel M.; **Proft, Thomas**; Wahid, Faisal; Cohen, Jonathan; **Fraser, John D.**; Sriskandan, Shiranee (1)
CS (1) Department of Infectious Diseases, Faculty of Medicine, Hammersmith Hospital, Imperial College School of Science, Technology, and Medicine, Du Cane Road, London, W12 0NN: s.sriskandan@ic.ac.uk UK
SO Journal of Immunology, (September 1, 2002) Vol. 169, No. 5, pp. 2561-2569. <http://www.jimmunol.org/>. print.
ISSN: 0022-1767.
DT Article
LA English
AB The gene encoding **streptococcal** mitogenic exotoxin Z (**SMEZ**) was disrupted in **Streptococcus** pyogenes. Despite the presence of other **superantigen** genes, mitogenic responses in

human and murine HLA-DQ transgenic cells were abrogated when cells were stimulated with supernatant from the **smez**- mutant compared with the parent strain. Remarkably, disruption of **smez** led to a complete inability to elicit cytokine production (TNF-alpha, lymphotoxin-alpha, IFN-gamma, IL-1 and -8) from human cells, when cocultured with **streptococcal** supernatants. The potent effects of **SMEZ** were apparent even though transcription and expression of **SMEZ** were barely detectable. Human Vbeta8+ T cell proliferation in response to *S. pyogenes* was **SMEZ**-dependent. Cells from HLA-DQ8 transgenic mice were 3 logs more sensitive to **SMEZ**-13 than cells from HLA-DR1 transgenic or wild-type mice. In the mouse, **SMEZ** targeted the human Vbeta8+ TCR homologue, murine Vbetall, at the expense of other TCR T cell subsets. Expression of **SMEZ** did not affect bacterial clearance or survival from peritoneal **streptococcal** infection in HLA-DQ8 mice, though effects of **SMEZ** on pharyngeal infection are unknown. Infection did lead to a rise in Vbetall+ T cells in the spleen which was partly reversed by disruption of the **smez** gene. Most strikingly, a clear rise in murine Vbeta4+ cells was seen in mice infected with the **smez**- mutant *S. pyogenes* strain, indicating a potential role for **SMEZ** as a repressor of cognate anti-**streptococcal** responses.

L7 ANSWER 3 OF 9 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 2
 AN 2001:345369 BIOSIS
 DN PREV200100345369
 TI Pyrogenicity and cytokine-inducing properties of **Streptococcus** pyogenes superantigens: Comparative study of **streptococcal** mitogenic exotoxin Z and pyrogenic exotoxin A.
 AU Muller-Alouf, Heide; **Proft, Thomas**; Zollner, Thomas M.; Gerlach, Dieter; Champagne, Eric; Desreumaux, Pierre; Fitting, Catherine; Geoffroy-Fauvet, Christiane; Alouf, Joseph E.; Cavaillon, Jean-Marc (1)
 CS (1) Department of Physiopathology, Institut Pasteur, 28 Rue Docteur Roux, 75015, Paris: jmcavail@pasteur.fr France
 SO Infection and Immunity, (June, 2001) Vol. 69, No. 6, pp. 4141-4145. print. ISSN: 0019-9567.
 DT Article
 LA English
 SL English
 AB **Streptococcal** mitogenic exotoxin Z (**SMEZ**), a superantigen derived from **Streptococcus** pyogenes, provoked expansion of human lymphocytes expressing the Vbeta 2, 4, 7 and 8 motifs of T-cell receptor. **SMEZ** was pyrogenic in rabbits and stimulated the expression of the T-cell activation markers CD69 and cutaneous lymphocyte-associated antigen. A variety of cytokines was released by human mononuclear leukocytes stimulated with **SMEZ**, which was 10-fold more active than **streptococcal** pyrogenic exotoxin A. Th2-derived cytokines were elicited only by superantigens and not by **streptococcal** cells.

L7 ANSWER 4 OF 9 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
 AN 2002:188931 BIOSIS
 DN PREV200200188931
 TI Molecular analysis of the immunological role of **streptococcal** mitogenic exotoxin Z.
 AU Unnikrishnan, M. (1); Altmann, D. (1); **Proft, T.**; Fraser, J. D.; Cohen, J. (1); Sriskandan, S. (1)
 CS (1) Imperial College School of Medicine, London UK
 SO Abstracts of the General Meeting of the American Society for Microbiology, (2001) Vol. 101, pp. 280. <http://www.asmsusa.org/mtgsrc/generalmeeting.htm>. print.
 Meeting Info.: 101st General Meeting of the American Society for Microbiology Orlando, FL, USA May 20-24, 2001

ISSN: 1060-2011.

DT Conference

LA English

AB **Streptococcal** mitogenic exotoxin Z is the most potent bacterial **superantigen** discovered to date. The biological function of **SMEZ** is unclear, but it may play a critical role in **streptococcal** pathogenesis; the gene is present in all strains studied and demonstrates extensive allelic variation. Aim: To characterize the immunological role of **SMEZ** in vitro and in vivo. Methods: **SmeZ** was insertionally inactivated in a clinical **Streptococcus** pyogenes strain, H293, to create strain H377. Proliferation of human PBMC, murine BALB/c, and HLA class II transgenic mouse splenocytes in response to purified rSMEZ, **SMEZ+** and **SMEZ-**culture supernatants was measured by thymidine incorporation. Analysis of TCR Vbeta bearing T cell populations was performed by flow cytometry in human and murine cells. Mice were infected i.p. with either H293 or H377 and TCR Vbeta repertoire changes in spleen T cells were measured following infection. Results: Targeted disruption of **smeZ** was confirmed by Southern hybridisation and PCR. Despite the low level of expression of **SMEZ** in H293, disruption of **smeZ** led to a six-fold diminution of T cell proliferation in supernatant-stimulated human PBMC and a specific reduction in expansion of Vbeta8+ T cells. BALB/c mice splenocytes were poorly responsive to rSMEZ and did not proliferate in response to H293 or H377 supernatant. HLA-DQ transgenic murine spleen cells were highly responsive to rSMEZ compared with wild type and HLA-DR transgenic mice cells. HLA-DQ spleen cells were also highly responsive to H293 supernatant; proliferation was abolished by disruption of **smeZ** rSMEZ caused specific expansion of murine TCR Vbetall+ (human TCR Vbeta8 gene homolog) T cells. In vivo experiments demonstrated expansion of mTCR Vbetall cells following infection with H293 in spleen; this expansion was significantly reduced in mice infected with H377 in the spleen, confirming that **SMEZ** can cause a **superantigen** effect in vivo, in invasive murine **streptococcal** sepsis. Conclusion: We clearly demonstrate the potency and TCR Vbeta-specific effects of **SMEZ**. Our results suggest a definite role for this **superantigen** in **streptococcal** pathogenesis.

L7 ANSWER 5 OF 9 WPIDS (C) 2003 THOMSON DERWENT DUPLICATE 3

AN 2000-452370 [39] WPIDS

DNC C2000-137919

TI Novel superantigens from **streptococcus** pyogenes useful for genotyping **streptococcus** pyogenes clones expressing **SMEZ** -2 and for diagnosing a Kawasaki syndrome.

DC B04 D16

IN FRASER, J D; PROFT, T

PA (AUCK-N) AUCKLAND UNISERVICES LTD

CYC 91

PI WO 2000039159 A1 20000706 (200039)* EN 72p

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL
OA PT SD SE SL SZ TZ UG ZW

W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES
FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS
LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL
TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

AU 2000019010 A 20000731 (200050)

EP 1141000 A1 20011010 (200167) EN

R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT
RO SE SI

JP 2002535966 W 20021029 (200274) 89p

ADT WO 2000039159 A1 WO 1999-NZ228 19991224; AU 2000019010 A AU 2000-19010
19991224; EP 1141000 A1 EP 1999-962603 19991224; WO 1999-NZ228 19991224;
JP 2002535966 W WO 1999-NZ228 19991224, JP 2000-591070 19991224

FDT AU 2000019010 A Based on WO 200039159; EP 1141000 A1 Based on WO 200039159; JP 2002535966 W Based on WO 200039159

PRAI NZ 1998-333589 19981224

AB WO 200039159 A UPAB: 20000818

NOVELTY - A **superantigen** (I) **SMEZ-2**, SPE-G, SPE-H or SPE-J, or its functionally equivalent variant, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) **SMEZ-2**, SPE-G, SPE-H, or SPE-J, having a 233, 234, 236, or 137 residue amino acid sequence, respectively, all fully defined in the specification;

(2) a polynucleotide (II) encoding (I), having a 702, 705, 711 or 414 nucleotide sequence, all fully defined in the specification, and encoding **SMEZ-2**, SPE-G, SPE-H, or SPE-J, respectively;

(3) a construct (III) comprising (I) and a cell-targeting molecule;

(4) a pharmaceutical composition comprising (III);

(5) an antibody (IV) which binds to (I);

(6) a nucleic acid molecule (V) which hybridizes to (II); and

(7) a kit which includes (II).

ACTIVITY - Cytostatic. No biological data given.

MECHANISM OF ACTION - T cell mitogens.

USE - (I) or (II) is used for subtyping **Streptococci** (claimed). They are also used for diagnosing a disease which is caused or mediated by expression of (I), in which the presence of (I) or (II) is detected by (IV) or (V), respectively, (claimed). The superantigens are used in diagnosis of disease such as Kawasaki syndrome. (II) can be used to design probes and primers for probing or amplifying parts of the **smez-2**, **spe-g**, **spe-h**, **spe-j** genes. They are also useful to recruit and activate T cells in a relatively non-specific fashion since they bind a large number of T cell receptor molecules by binding to the V beta domain. The constructs are useful in cancer therapy.

Dwg.0/13

L7 ANSWER 6 OF 9 BIOTECHDS COPYRIGHT 2003 THOMSON DERWENT AND ISI

AN 2000-12141 BIOTECHDS

TI Novel superantigens from **Streptococcus** sp. pyogenes useful for genotyping **Streptococcus** pyogenes clones expressing **SMEZ-2** and for diagnosing a Kawasaki syndrome; recombinant **superantigen** production and DNA probe, DNA primer and antibody for Kawasaki syndrome and disease diagnosis and therapy

AU Fraser J D; Proft T

PA Auckland-Uniservices

LO Auckland, New Zealand.

PI WO 2000039159 6 Jul 2000

AI WO 1999-NZ228 24 Dec 1999

PRAI NZ 1998-333589 24 Dec 1998

DT Patent

LA English

OS WPI: 2000-452370 [39]

AB A **Streptococcus** pyogenes **superantigen** (I)

SMEZ-2, SPE-G, SPE-H or SPE-J, or its functionally equivalent variant, is claimed. Also claimed are: **SMEZ-2**, SPE-G, SPE-H or SPE-J, having a 233, 234, 236 or 137 amino acid protein sequence (specified), respectively; a DNA (II) encoding (I), having a 702, 705, 711 or 414 DNA sequence (specified), and encoding **SMEZ-2**, SPE-G, SPE-H or SPE-J, respectively; a construct (III) with (I) and a cell-targeting molecule; a pharmaceutical composition with (III); an antibody (IV) which binds to (I); a DNA probe (V) which hybridizes to (II); and a kit which has (II). (I) or (II) is used for subtyping **streptococci**. They are also used for diagnosing disease which is caused or mediated by expression of (I), in which the presence of (I) or (II) is detected by (IV) or (V), respectively. The superantigens are

used in diagnosis of disease such as Kawasaki syndrome. (II) can be used to design DNA probes and DNA primers for probing or amplifying parts of the **smez-2**, **spe-g**, **spe-h**, **spe-j** genes. They are also useful to recruit and activate T-lymphocytes in a relatively non-specific manner. The constructs are useful in cancer therapy. (72pp)

L7 ANSWER 7 OF 9 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 4
AN 2000:293069 BIOSIS
DN PREV200000293069

TI The **streptococcal superantigen SMEZ** exhibits wide allelic variation, mosaic structure, and significant antigenic variation.

AU **Proft, Thomas**; Moffatt, S. Louise; Weller, Kylie D.; Paterson, A.; Martin, Diana; **Fraser, John D.** (1)

CS (1) Department of Molecular Medicine, School of Medicine, University of Auckland, Auckland New Zealand

SO Journal of Experimental Medicine, (May 15, 2000) Vol. 191, No. 10, pp. 1765-1776. print.
ISSN: 0022-1007.

DT Article

LA English

SL English

AB The frequencies of the newly identified **streptococcal superantigen** genes **smez**, **spe-g**, and **spe-h** were determined in a panel of 103 clinical isolates collected between 1976 and 1998 at various locations throughout New Zealand. **smez** and **spe-g** were found in every group A **Streptococcus** (GAS) isolate, suggesting a chromosomal location. The **spe-h** gene was found in only 24% of the GAS isolates and is probably located on a mobile DNA element. The **smez** gene displays extensive allelic variation and appears to be in linkage equilibrium with the M/emm type. 22 novel **smez** alleles were identified from 21 different M/emm types in addition to the already reported alleles **smez** and **smez-2** with sequence identities between 94.5 and 99.9%. Three alleles are nonfunctional due to a single base pair deletion. The remaining 21 alleles encode distinct **SMEZ** variants. The mosaic structure of the **smez** gene suggests that this polymorphism has arisen from homologous recombination events rather than random point mutation. The recently resolved **SMEZ-2** crystal structure shows that the polymorphic residues are mainly surface exposed and scattered over the entire protein. The allelic variation did not affect either Vbeta specificity or potency, but did result in significant antigenic differences. Neutralizing antibody responses of individual human sera against different **SMEZ** variants varied significantly. 98% of sera completely neutralized **SMEZ-1**, but only 85% neutralized **SMEZ-2**, a very potent variant that has not yet been found in any New Zealand isolate. **SMEZ**-specific Vbeta8 activity was found in culture supernatants of 66% of the GAS isolates, indicating a potential base for the development of a **SMEZ** targeting vaccine.

L7 ANSWER 8 OF 9 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 5
AN 2000:375574 BIOSIS
DN PREV200000375574

TI Conservation and variation in **superantigen** structure and activity highlighted by the three-dimensional structures of two new superantigens from **Streptococcus pyogenes**.

AU Arcus, Vickery L.; **Proft, Thomas**; Sigrell, Jill A.; Baker, Heather M.; **Fraser, John D.**; Baker, Edward N. (1)

CS (1) School of Biological Sciences, University of Auckland, Auckland New Zealand

SO Journal of Molecular Biology, (26 May, 2000) Vol. 299, No. 1, pp. 157-168. print.
ISSN: 0022-2836.

DT Article
 LA English
 SL English
 AB Bacterial superantigens (SAGs) are a structurally related group of protein toxins secreted by *Staphylococcus aureus* and ***Streptococcus pyogenes***. They are implicated in a range of human pathologies associated with bacterial infection whose symptoms result from SAG-mediated stimulation of a large number (2-20%) of T-cells. At the molecular level, bacterial SAGs bind to major histocompatibility class II (MHC-II) molecules and disrupt the normal interaction between MHC-II and T-cell receptors (TCRs). We have determined high-resolution crystal structures of two newly identified **streptococcal** superantigens, SPE-H and **SMEZ-2**. Both structures conform to the generic bacterial **superantigen** folding pattern, comprising an OB-fold N-terminal domain and a beta-grasp C-terminal domain. SPE-H and **SMEZ-2** also display very similar zinc-binding sites on the outer concave surfaces of their C-terminal domains. Structural comparisons with other SAGs identify two structural sub-families. Sub-families are related by conserved core residues and demarcated by variable binding surfaces for MHC-II and TCR. **SMEZ-2** is most closely related to the **streptococcal** SAG SPE-C, and together they constitute one structural sub-family. In contrast, SPE-H appears to be a hybrid whose N-terminal domain is most closely related to the SEB sub-family and whose C-terminal domain is most closely related to the SPE-C/**SMEZ-2** sub-family. MHC-II binding for both SPE-H and **SMEZ-2** is mediated by the zinc ion at their C-terminal face, whereas the generic N-terminal domain MHC-II binding site found on many SAGs appears not to be present. Structural comparisons provide evidence for variations in TCR binding between SPE-H, **SMEZ-2** and other members of the SAG family; the extreme potency of **SMEZ-2** (active at 10-15 g ml⁻¹ levels) is likely to be related to its TCR binding properties. The **smez** gene shows allelic variation that maps onto a considerable proportion of the protein surface. This allelic variation, coupled with the varied binding modes of SAGs to MHC-II and TCR, highlights the pressure on SAGs to avoid host immune defences.

L7 ANSWER 9 OF 9 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 6
 AN 1999:98436 BIOSIS
 DN PREV199900098436
 TI Identification and characterization of novel superantigens from ***Streptococcus pyogenes***.
 AU Proft, Thomas ; Moffatt, S. Louise; Berkahn, Celia J.;
 Fraser, John D. (1)
 CS (1) Dep. Mol. Med., Sch. Med., Univ. Auckland, Private Bag 92019, Auckland New Zealand
 SO Journal of Experimental Medicine, (Jan. 4, 1999) Vol. 189, No. 1, pp. 89-101.
 ISSN: 0022-1007.

DT Article
 LA English
 AB Three novel **streptococcal superantigen** genes (spe-g, spe-h, and spe-j) were identified from the ***Streptococcus pyogenes*** M1 genomic database at the University of Oklahoma. A fourth novel gene (**smez-2**) was isolated from the *S. pyogenes* strain 2035, based on sequence homology to the **streptococcal** mitogenic exotoxin z (**smez**) gene. **SMEZ-2**, SPE-G, and SPE-J are most closely related to **SMEZ** and **streptococcal** pyrogenic exotoxin (SPE)-C, whereas SPE-H is most similar to the staphylococcal toxins than to any other **streptococcal** toxin. Recombinant (r)**SMEZ**, r**SMEZ-2**, rSPE-G, and rSPE-H were mitogenic for human peripheral blood lymphocytes with half-maximal responses between 0.02 and 50 pg/ml (r**SMEZ-2** and rSPE-H, respectively). **SMEZ-2** is the most potent **superantigen** (SAG) discovered thus far. All

toxins, except rSPE-G, were active on murine T cells, but with reduced potency. Binding to a human B-lymphoblastoid line was shown to be zinc dependent with high binding affinity of 15-65 nM. Evidence from modeled protein structures and competitive binding experiments suggest that high affinity binding of each toxin is to the major histocompatibility complex class II beta chain. Competition for binding between toxins was varied and revealed overlapping but discrete binding to subsets of class II molecules in the hierarchical order (**SMEZ**, SPE-C) > **SMEZ-2** > SPE-H > SPE-G. The most common targets for the novel SAGs were human Vbeta2.1- and Vbeta4-expressing T cells. This might reflect a specific role for this subset of Vbetas in the immune defense of gram-positive bacteria.

=> s streptococc? mitogenic exotoxin
L8 30 STREPTOCOCC? MITOGENIC EXOTOXIN

=> s 18 and superantigen
L9 26 L8 AND SUPERANTIGEN

=> dup rem 19
PROCESSING COMPLETED FOR L9
L10 10 DUP REM L9 (16 DUPLICATES REMOVED)

=> d bib ab 1-10

L10 ANSWER 1 OF 10 CAPLUS COPYRIGHT 2003 ACS
AN 2003:22707 CAPLUS
DN 138:88639
TI Bacterial **superantigen**-antibody conjugates for treating human
proliferative diseases or cancers
IN Forsberg, Goeran; Erlandsson, Eva; Antonsson, Per; Walse, Bjoern
PA Active Biotech AB, Swed.
SO PCT Int. Appl., 102 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2003002143	A1	20030109	WO 2002-SE1188	20020619
	W:		AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, VZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG		
	RW:		GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG		
	US 2003039655	A1	20030227	US 2001-900766	20010706
PRAI	SE 2001-2327	A	20010628		

AB The present invention relates to compns. and methods of use, wherein the compn. comprises a conjugate of a bacterial **superantigen** and an antibody moiety. More particularly, the bacterial **superantigen** has been modified to decrease seroreactivity with retained **superantigen** activity. The bacterial **superantigen** is staphylococcal enterotoxin (SE), Streptococcus pyogenes exotoxin (SPE), Staphylococcus aureus toxic shock-syndrome toxin (TSST-1), **streptococcal mitogenic exotoxin** (SME) or **superantigen** (SSA), Staphylococcal enterotoxin A (SEA) or E (SEE). The antibody or active fragment is directed against a cancer-assocd. cell

surface structure. The **superantigen**-antibody conjugates are used for treating lung, breast, colon, kidney, pancreatic, ovarian, stomach, cervix and prostate cancer. The **superantigen**-antibody conjugates may optionally combine with cytokine such as interleukin esp. interleukin 2 for i.v. administration.

RE.CNT 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 2 OF 10 USPATFULL

AN 2003:57091 USPATFULL

TI Novel engineered **superantigen** for human therapy

IN Forsberg, Goran, Eslov, SWEDEN

Erlandsson, Eva, Dalby, SWEDEN

Antonsson, Per, Lund, SWEDEN

Walse, Bjorn, Lund, SWEDEN

PI US 2003039655 A1 20030227

AI US 2001-900766 A1 20010706 (9)

PRAI SE 2001-2327 20010628

DT Utility

FS APPLICATION

LREP FULBRIGHT & JAWORSKI L.L.P., Melissa W. Acosta, Suite 5100, 1301

McKinney, Houston, TX, 77010-3095

CLMN Number of Claims: 92

ECL Exemplary Claim: 1

DRWN 11 Drawing Page(s)

LN.CNT 2525

AB The present invention relates to compositions and methods of use, wherein the composition comprises a conjugate of a bacterial **superantigen** and an antibody moiety. More particularly, the bacterial **superantigen** has been modified to decrease seroreactivity with retained **superantigen** activity.

L10 ANSWER 3 OF 10 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
1

AN 2002:513642 BIOSIS

DN PREV200200513642

TI The bacterial **superantigen streptococcal mitogenic exotoxin Z** is the major immunoactive agent of *Streptococcus pyogenes*.

AU Unnikrishnan, Meera; Altmann, Daniel M.; Proft, Thomas; Wahid, Faisal; Cohen, Jonathan; Fraser, John D.; Sriskandan, Shiranee (1)

CS (1) Department of Infectious Diseases, Faculty of Medicine, Hammersmith Hospital, Imperial College School of Science, Technology, and Medicine, Du Cane Road, London, W12 0NN: s.sriskandan@ic.ac.uk UK

SO Journal of Immunology, (September 1, 2002) Vol. 169, No. 5, pp. 2561-2569.
<http://www.jimmunol.org/>. print.
ISSN: 0022-1767.

DT Article

LA English

AB The gene encoding **streptococcal mitogenic exotoxin Z** (SMEZ) was disrupted in *Streptococcus pyogenes*. Despite the presence of other **superantigen** genes, mitogenic responses in human and murine HLA-DQ transgenic cells were abrogated when cells were stimulated with supernatant from the smeZ- mutant compared with the parent strain. Remarkably, disruption of smeZ led to a complete inability to elicit cytokine production (TNF-alpha, lymphotoxin-alpha, IFN-gamma, IL-1 and -8) from human cells, when cocultured with streptococcal supernatants. The potent effects of SMEZ were apparent even though transcription and expression of SMEZ were barely detectable. Human Vbeta8+ T cell proliferation in response to *S. pyogenes* was SMEZ-dependent. Cells from HLA-DQ8 transgenic mice were 3 logs more sensitive to SMEZ-13 than cells from HLA-DR1 transgenic or wild-type mice. In the mouse, SMEZ targeted the human Vbeta8+ TCR homologue, murine Vbeta11, at the expense of other TCR T

cell subsets. Expression of SMEZ did not affect bacterial clearance or survival from peritoneal streptococcal infection in HLA-DQ8 mice, though effects of SMEZ on pharyngeal infection are unknown. Infection did lead to a rise in Vbetall+ T cells in the spleen which was partly reversed by disruption of the smeZ gene. Most strikingly, a clear rise in murine Vbeta4+ cells was seen in mice infected with the smeZ- mutant *S. pyogenes* strain, indicating a potential role for SMEZ as a repressor of cognate anti-streptococcal responses.

L10 ANSWER 4 OF 10 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
2

AN 2001:345369 BIOSIS

DN PREV200100345369

TI Pyrogenicity and cytokine-inducing properties of *Streptococcus pyogenes* superantigens: Comparative study of **streptococcal**

mitogenic exotoxin Z and pyrogenic exotoxin A.

AU Muller-Alouf, Heide; Proft, Thomas; Zollner, Thomas M.; Gerlach, Dieter; Champagne, Eric; Desreumaux, Pierre; Fitting, Catherine; Geoffroy-Fauvet, Christiane; Alouf, Joseph E.; Cavaillon, Jean-Marc (1)

CS (1) Department of Physiopathology, Institut Pasteur, 28 Rue Docteur Roux, 75015, Paris: jmcavail@pasteur.fr France

SO Infection and Immunity, (June, 2001) Vol. 69, No. 6, pp. 4141-4145. print. ISSN: 0019-9567.

DT Article

LA English

SL English

AB **Streptococcal mitogenic exotoxin Z (SMEZ)**, a **superantigen** derived from *Streptococcus pyogenes*, provoked expansion of human lymphocytes expressing the Vbeta 2, 4, 7 and 8 motifs of T-cell receptor. SMEZ was pyrogenic in rabbits and stimulated the expression of the T-cell activation markers CD69 and cutaneous lymphocyte-associated antigen. A variety of cytokines was released by human mononuclear leukocytes stimulated with SMEZ, which was 10-fold more active than streptococcal pyrogenic exotoxin A. Th2-derived cytokines were elicited only by superantigens and not by streptococcal cells.

L10 ANSWER 5 OF 10 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
3

AN 2001:195993 BIOSIS

DN PREV200100195993

TI Functional characterization of streptococcal pyrogenic exotoxin J, a novel **superantigen**.

AU McCormick, John K.; Pragman, Alexa A.; Stolpa, John C.; Leung, Donald Y. M.; Schlievert, Patrick M. (1)

CS (1) Department of Microbiology, University of Minnesota Medical School, 420 Delaware St., S.E, Minneapolis, MN, 55455: pats@lenti.med.umn.edu USA

SO Infection and Immunity, (March, 2001) Vol. 69, No. 3, pp. 1381-1388. print.

ISSN: 0019-9567.

DT Article

LA English

SL English

AB Streptococcal toxic syndrome (STSS) is a highly lethal, acute-onset illness that is a subset of invasive streptococcal disease. The majority of clinical STSS cases have been associated with the pyrogenic toxin superantigens (PTSAGs) streptococcal pyrogenic exotoxin A or C (SPE A or C), although cases have been reported that are not associated with either of these exotoxins. Recent genome sequencing projects have revealed a number of open reading frames that potentially encode proteins with similarity to SPEs A and C and to other PTSAGs. Here, we describe the cloning, expression, purification, and functional characterization of a novel exotoxin termed streptococcal pyrogenic exotoxin J (SPE J). Purified recombinant SPE J (rSPE J) expressed from *Escherichia coli* stimulated the

expansion of both rabbit splenocytes and human peripheral blood lymphocytes, preferentially expanded human T cells displaying Vbeta2, -3, -12, -14, and -17 on their T-cell receptors, and was active at concentrations as low as 5×10^{-6} mug/ml. Furthermore, rSPE J induced fevers in rabbits and was lethal in two models of STSS. Biochemically, SPE J had a predicted molecular weight of 24,444 and an isoelectric point of 7.7 and lacked the ability to form the cystine loop structure characteristic of many PTSAGs. SPE J shared 19.6, 47.1, 38.8, 18.1, 19.6, and 24.4% identity with SPEs A, C, G, and H, streptococcal **superantigen**, and **streptococcal mitogenic exotoxin Z-2**, respectively, and was immunologically cross-reactive with SPE C. The characterization of a seventh functional streptococcal PTSAG raises important questions relating to the evolution of the streptococcal superantigens.

- L10 ANSWER 6 OF 10 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
 AN 2002:293446 BIOSIS
 DN PREV200200293446
 TI Evidence for **superantigen** involvement in severe group A streptococcal tissue infections.
 AU Norrby-Teglund, Anna (1); Thulin, Pontus; Gan, Bing S.; Kotb, Malak; McGeer, Allison; Andersson, Jan; Low, Donald E.
 CS (1) Center for Infectious Medicine, Karolinska Institutet, Dept. of Medicine-I63, Huddinge University Hospital, SE-141 86, Stockholm: Anna.Norrby-Teglund@medhs.ki.se Sweden
 SO Journal of Infectious Diseases, (1 October, 2001) Vol. 184, No. 7, pp. 853-860. print.
 ISSN: 0022-1899.
 DT Article
 LA English
 AB Host-pathogen interactions were studied in tissue biopsy samples from patients with severe invasive group A streptococcus (GAS) infections. Skin, subcutaneous tissue, and fascia biopsy samples were divided into clinical grade 1 (no evidence of inflammation (n = 7)) or clinical grade 2 (inflamed tissue-erythema and edema including cellulitis, fasciitis, and necrotizing fasciitis (n = 24)). In situ imaging demonstrated significantly higher bacterial load in biopsy samples of higher clinical grade ($P < .05$), and the bacterial load correlated with the in vivo expression of the **superantigen** streptococcal pyrogenic exotoxin F ($P < .02$). Increased expression of the interleukin-1 cytokines and significantly higher expression of tumor necrosis factor-beta, interferon-gamma, and the homing receptors CC chemokine receptor 5, CD44, and cutaneous lymphocyte-associated antigen ($P < .002-.05$) were observed in biopsy samples of higher clinical grade. Thus, the cytokine profile at the local site of infection mimics that of a typical **superantigen** cytokine response. The findings of this study demonstrate a critical role for superantigens and Th1 cytokines in GAS tissue infections.
- L10 ANSWER 7 OF 10 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
 AN 2002:188931 BIOSIS
 DN PREV200200188931
 TI Molecular analysis of the immunological role of **streptococcal mitogenic exotoxin Z**.
 AU Unnikrishnan, M. (1); Altmann, D. (1); Proft, T.; Fraser, J. D.; Cohen, J. (1); Sriskandan, S. (1)
 CS (1) Imperial College School of Medicine, London UK
 SO Abstracts of the General Meeting of the American Society for Microbiology, (2001) Vol. 101, pp. 280. <http://www.asmtg.org/mtgsrc/generalmeeting.htm>. print.
 Meeting Info.: 101st General Meeting of the American Society for Microbiology Orlando, FL, USA May 20-24, 2001
 ISSN: 1060-2011.
 DT Conference

LA English

AB **Streptococcal mitogenic exotoxin Z** is the most potent bacterial **superantigen** discovered to date. The biological function of SMEZ is unclear, but it may play a critical role in streptococcal pathogenesis; the gene is present in all strains studied and demonstrates extensive allelic variation. Aim: To characterize the immunological role of SMEZ in vitro and in vivo. Methods: SmeZ was insertionally inactivated in a clinical Streptococcus pyogenes strain, H293, to create strain H377. Proliferation of human PBMC, murine BALB/c, and HLA class II transgenic mouse splenocytes in response to purified rSMEZ, SMEZ+ and SMEZ-culture supernatants was measured by thymidine incorporation. Analysis of TCR Vbeta bearing T cell populations was performed by flow cytometry in human and murine cells. Mice were infected i.p. with either H293 or H377 and TCR Vbeta repertoire changes in spleen T cells were measured following infection. Results: Targeted disruption of smeZ was confirmed by Southern hybridisation and PCR. Despite the low level of expression of SMEZ in H293, disruption of smeZ led to a six-fold diminution of T cell proliferation in supernatant-stimulated human PBMC and a specific reduction in expansion of Vbeta8+ T cells. BALB/c mice splenocytes were poorly responsive to rSMEZ and did not proliferate in response to H293 or H377 supernatant. HLA-DQ transgenic murine spleen cells were highly responsive to rSMEZ compared with wild type and HLA-DR transgenic mice cells. HLA-DQ spleen cells were also highly responsive to H293 supernatant; proliferation was abolished by disruption of smeZ rSMEZ caused specific expansion of murine TCR Vbetall+ (human TCR Vbeta8 gene homolog) T cells. In vivo experiments demonstrated expansion of mTCR Vbetall cells following infection with H293 in spleen; this expansion was significantly reduced in mice infected with H377 in the spleen, confirming that SMEZ can cause a **superantigen** effect in vivo, in invasive murine streptococcal sepsis. Conclusion: We clearly demonstrate the potency and TCR Vbeta-specific effects of SMEZ. Our results suggest a definite role for this **superantigen** in streptococcal pathogenesis.

L10 ANSWER 8 OF 10 CAPLUS COPYRIGHT 2003 ACS

AN 2000:455127 CAPLUS

DN 134:13824

TI Purification and biochemical characterization of a basic **superantigen** (SPEX/SMEZ3) from Streptococcus pyogenes

AU Gerlach, D.; Fleischer, B.; Wagner, M.; Schmidt, K.-H.; Vettermann, S.; Reichardt, W.

CS Institute of Medical Microbiology, Friedrich-Schiller-University Jena, Jena, D-07740, Germany

SO FEMS Microbiology Letters (2000), 188(2), 153-163

CODEN: FMLED7; ISSN: 0378-1097

PB Elsevier Science B.V.

DT Journal

LA English

AB A potent basic **superantigen** (designated streptococcal pyrogenic exotoxin X, SPEX/SMEZ3) was purified to homogeneity from culture supernatants of a Streptococcus pyogenes scarlatina strain of type 12 (genotype speA-, speC-) and characterized. Sequence alignments revealed SPEX to be an allele of the streptococcal mitogens type Z (SMEZ). The N-terminal amino acid sequence of SPEX was found with LEVDNNSLLR to be identical to the recently described acidic **superantigen** SMEZ. Although SPEX/SMEZ genes were present in all of the streptococcal strains tested, a toxin prodn. could only be detected in a small no. of strains. The produced toxin concn. in the culture supernatants of pos. strains differed between 0 and 20 ng ml⁻¹. The purified SPEX stimulated human T-lymphocytes with V.beta.8 specificity at extremely low concns. (lower than 100 pg ml⁻¹).

RE.CNT 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 9 OF 10 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
4
AN 1999:98436 BIOSIS
DN PREV199900098436
TI Identification and characterization of novel superantigens from
Streptococcus pyogenes.
AU Proft, Thomas ; Moffatt, S. Louise; Berkahn, Celia J.; Fraser, John D. (1)
CS (1) Dep. Mol. Med., Sch. Med., Univ. Auckland, Private Bag 92019, Auckland
New Zealand
SO Journal of Experimental Medicine, (Jan. 4, 1999) Vol. 189, No. 1, pp.
89-101.
ISSN: 0022-1007.
DT Article
LA English
AB Three novel streptococcal **superantigen** genes (spe-g, spe-h, and
spe-j) were identified from the Streptococcus pyogenes M1 genomic database
at the University of Oklahoma. A fourth novel gene (smez-2) was isolated
from the S. pyogenes strain 2035, based on sequence homology to the
streptococcal mitogenic exotoxin z (smez)
gene. SMEZ-2, SPE-G, and SPE-J are most closely related to SMEZ and
streptococcal pyrogenic exotoxin (SPE)-C, whereas SPE-H is most similar to
the staphylococcal toxins than to any other streptococcal toxin.
Recombinant (r)SMEZ, rSMEZ-2, rSPE-G, and rSPE-H were mitogenic for human
peripheral blood lymphocytes with half-maximal responses between 0.02 and
50 pg/ml (rSMEZ-2 and rSPE-H, respectively). SMEZ-2 is the most potent
superantigen (SAG) discovered thus far. All toxins, except rSPE-G,
were active on murine T cells, but with reduced potency. Binding to a
human B-lymphoblastoid line was shown to be zinc dependent with high
binding affinity of 15-65 nM. Evidence from modeled protein structures and
competitive binding experiments suggest that high affinity binding of each
toxin is to the major histocompatibility complex class II beta chain.
Competition for binding between toxins was varied and revealed overlapping
but discrete binding to subsets of class II molecules in the hierarchical
order (SMEZ, SPE-C) > SMEZ-2 > SPE-H > SPE-G. The most common targets for
the novel SAGs were human Vbeta2.1- and Vbeta4-expressing T cells. This
might reflect a specific role for this subset of Vbetas in the immune
defense of gram-positive bacteria.

L10 ANSWER 10 OF 10 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 97286629 EMBASE
DN 1997286629
TI **Streptococcal mitogenic exotoxin Z**, a novel
acidic superantigenic toxin produced by a T1 strain of Streptococcus
pyogenes.
AU Kamezawa Y.; Nakahara T.; Nakano S.; Abe Y.; Nozaki-Renard J.; Isono T.
CS Y. Abe, Department of Pathology, Teikyo Univ. School of Medicine, Kaga
2-11-1, Itabashi-ku, Tokyo 173, Japan. a125025y@med.teikyo-u.ac.jp
SO Infection and Immunity, (1997) 65/9 (3828-3833).
Refs: 41
ISSN: 0019-9567 CODEN: INFIBR
CY United States
DT Journal; Article
FS 004 Microbiology
LA English
SL English
AB Streptococcus pyogenes T1 was previously found to produce an acidic
mitogenic exotoxin, designated A.beta., antigenically distinct from
erythrogenic toxin type A (ETA) of strains T1 and NY5. Following chemical
analysis and biological characterization, we have renamed this toxin
streptococcal mitogenic exotoxin Z (SMEZ).
Physicochemical separation of SMEZ from ETA was successfully performed on
a hydrophobic chromatograph. The isoelectric point was pH 5.3, and the

molecular size was estimated to be 28 kDa. These values were similar to those of ETA, but the amino acid composition and the NH2-terminal sequence of SMEZ were distinct from those of any mitogenic exotoxins hitherto described. Its mitogenic activity was found to be more potent than that of ETA in rabbit lymphocyte cultures. A specific antiserum raised against SMEZ did not cross-react with ETA, ETB, or ETC in the neutralization tests of mitogenic and erythrogenic activities. Its superantigenic nature was evident from the reverse transcriptase PCR findings of the T-cell receptor V.beta. profiles of rabbit lymphocytes stimulated in vitro. The V.beta. 8 subfamily was unique to SMEZ, while the V.beta. 2 and 6 subfamilies were found to be common among lymphocytes stimulated with ETA, ETB, ETC, or SMEZ. The results from this study provide an additional example of the diversity that exists among mitogenic or superantigenic exotoxins of streptococcal origin.

=> FIL STNGUIDE

COST IN U.S. DOLLARS	SINCE FILE	TOTAL
	ENTRY	SESSION
FULL ESTIMATED COST	73.69	73.90

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE	TOTAL
	ENTRY	SESSION
CA SUBSCRIBER PRICE	-1.30	-1.30

FILE 'STNGUIDE' ENTERED AT 15:48:25 ON 03 MAR 2003
 USE IS SUBJECT TO THE TERMS OF YOUR CUSTOMER AGREEMENT
 COPYRIGHT (C) 2003 AMERICAN CHEMICAL SOCIETY, JAPAN SCIENCE
 AND TECHNOLOGY CORPORATION, AND FACHINFORMATIONSZENTRUM KARLSRUHE

FILE CONTAINS CURRENT INFORMATION.
 LAST RELOADED: Feb 28, 2003 (20030228/UP).

=> d his

(FILE 'HOME' ENTERED AT 15:41:36 ON 03 MAR 2003)

FILE 'BIOSIS, MEDLINE, AGRICOLA, EMBASE, CABA, WPIDS, JAPIO, BIOTECHDS,
 LIFESCI, CAPLUS, USPATFULL, USPAT2' ENTERED AT 15:41:51 ON 03 MAR 2003
 E PROFIT THOMAS/AU

L1	86 S E1-E3
	E FRASER JOHN D/AU
L2	87 S E3-E5
L3	156 S L1 OR L2
L4	66 S L3 AND SUPERANTIGEN
L5	38 S L4 AND STREPTOCOCC?
L6	30 S L5 AND SMEZ?
L7	9 DUP REM L6 (21 DUPLICATES REMOVED)
L8	30 S STREPTOCOCC? MITOGENIC EXOTOXIN
L9	26 S L8 AND SUPERANTIGEN
L10	10 DUP REM L9 (16 DUPLICATES REMOVED)

FILE 'STNGUIDE' ENTERED AT 15:48:25 ON 03 MAR 2003

=> dup rem 16

COST IN U.S. DOLLARS	SINCE FILE	TOTAL
	ENTRY	SESSION
FULL ESTIMATED COST	0.30	74.20

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE	TOTAL
	ENTRY	SESSION
CA SUBSCRIBER PRICE	0.00	-1.30

FILE 'BIOSIS' ENTERED AT 15:51:42 ON 03 MAR 2003
COPYRIGHT (C) 2003 BIOLOGICAL ABSTRACTS INC.(R)

FILE 'MEDLINE' ENTERED AT 15:51:42 ON 03 MAR 2003

FILE 'EMBASE' ENTERED AT 15:51:42 ON 03 MAR 2003
COPYRIGHT (C) 2003 Elsevier Science B.V. All rights reserved.

FILE 'WPIDS' ENTERED AT 15:51:42 ON 03 MAR 2003
COPYRIGHT (C) 2003 THOMSON DERWENT

FILE 'BIOTECHDS' ENTERED AT 15:51:42 ON 03 MAR 2003
COPYRIGHT (C) 2003 THOMSON DERWENT AND INSTITUTE FOR SCIENTIFIC INFORMATION

FILE 'LIFESCI' ENTERED AT 15:51:42 ON 03 MAR 2003
COPYRIGHT (C) 2003 Cambridge Scientific Abstracts (CSA)

FILE 'CAPLUS' ENTERED AT 15:51:42 ON 03 MAR 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2003 AMERICAN CHEMICAL SOCIETY (ACS)
PROCESSING COMPLETED FOR L6
L11 9 DUP REM L6 (21 DUPLICATES REMOVED)

=> d bib ab 1-9

L11 ANSWER 1 OF 9 MEDLINE
AN 2003084097 IN-PROCESS
DN 22483693 PubMed ID: 12595453
TI Two novel superantigens found in both group a and group C
streptococcus.
AU **Proft Thomas**; Webb Phillip D; Handley Vanessa; **Fraser John**
D
CS Department of Molecular Medicine and Pathology, Faculty of Medical and
Health Sciences, University of Auckland, Auckland, New Zealand.
SO INFECTION AND IMMUNITY, (2003 Mar) 71 (3) 1361-9.
Journal code: 0246127. ISSN: 0019-9567.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS IN-PROCESS; NONINDEXED; Priority Journals
ED Entered STN: 20030222
Last Updated on STN: 20030222
AB Two novel **streptococcal superantigen** genes (speL(Se)
and speM(Se)) were identified from the **Streptococcus equi** genome
database at the Sanger Center. Genotyping of 8 *S. equi* isolates and 40
Streptococcus pyogenes isolates resulted in the detection of the
orthologous genes speL and speM in a restricted number of *S. pyogenes*
isolates (15 and 5%, respectively). Surprisingly, the novel
superantigen genes could not be found in any of the analyzed *S.*
equi isolates. The results suggest that both genes are located on a mobile
element that enables gene transfer between individual isolates and between
streptococci from different Lancefield groups. *S. equi* pyrogenic
exotoxin L (SPE-L(Se))/**streptococcal** pyrogenic exotoxin L
(SPE-L) and SPE-M(Se)/SPE-M are most closely related to **SMEZ**,
SPE-C, SPE-G, and SPE-J, but build a separate branch within this group.
Recombinant SPE-L (rSPE-L) and rSPE-M were highly mitogenic for human
peripheral blood lymphocytes, with half-maximum responses at 1 and 10
pg/ml, respectively. The results from competitive binding experiments
suggest that both proteins bind major histocompatibility complex class II
at the beta-chain, but not at the alpha-chain. The most common targets for
both toxins were human Vbeta1.1 expressing T cells. Seroconversion against

SPE-L and SPE-M was observed in healthy blood donors, suggesting that the toxins are expressed in vivo. Interestingly, the speL gene is highly associated with *S. pyogenes* M89, a serotype that is linked to acute rheumatic fever in New Zealand.

L11 ANSWER 2 OF 9 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 1
AN 2002:513642 BIOSIS
DN PREV200200513642
TI The bacterial **superantigen streptococcal** mitogenic exotoxin Z is the major immunoactive agent of **Streptococcus pyogenes**.
AU Unnikrishnan, Meera; Altmann, Daniel M.; Proft, Thomas; Wahid, Faisal; Cohen, Jonathan; Fraser, John D.; Sriskandan, Shiranee (1)
CS (1) Department of Infectious Diseases, Faculty of Medicine, Hammersmith Hospital, Imperial College School of Science, Technology, and Medicine, Du Cane Road, London, W12 0NN: s.sriskandan@ic.ac.uk UK
SO Journal of Immunology, (September 1, 2002) Vol. 169, No. 5, pp. 2561-2569. <http://www.jimmunol.org/>. print. ISSN: 0022-1767.
DT Article
LA English
AB The gene encoding **streptococcal** mitogenic exotoxin Z (**SMEZ**) was disrupted in **Streptococcus pyogenes**. Despite the presence of other **superantigen** genes, mitogenic responses in human and murine HLA-DQ transgenic cells were abrogated when cells were stimulated with supernatant from the **smez**- mutant compared with the parent strain. Remarkably, disruption of **smez** led to a complete inability to elicit cytokine production (TNF-alpha, lymphotoxin-alpha, IFN-gamma, IL-1 and -8) from human cells, when cocultured with **streptococcal** supernatants. The potent effects of **SMEZ** were apparent even though transcription and expression of **SMEZ** were barely detectable. Human Vbeta8+ T cell proliferation in response to *S. pyogenes* was **SMEZ**-dependent. Cells from HLA-DQ8 transgenic mice were 3 logs more sensitive to **SMEZ**-13 than cells from HLA-DR1 transgenic or wild-type mice. In the mouse, **SMEZ** targeted the human Vbeta8+ TCR homologue, murine Vbetall, at the expense of other TCR T cell subsets. Expression of **SMEZ** did not affect bacterial clearance or survival from peritoneal **streptococcal** infection in HLA-DQ8 mice, though effects of **SMEZ** on pharyngeal infection are unknown. Infection did lead to a rise in Vbetall+ T cells in the spleen which was partly reversed by disruption of the **smez** gene. Most strikingly, a clear rise in murine Vbeta4+ cells was seen in mice infected with the **smez**- mutant *S. pyogenes* strain, indicating a potential role for **SMEZ** as a repressor of cognate anti-**streptococcal** responses.

L11 ANSWER 3 OF 9 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 2
AN 2001:345369 BIOSIS
DN PREV200100345369
TI Pyrogenicity and cytokine-inducing properties of **Streptococcus pyogenes** superantigens: Comparative study of **streptococcal** mitogenic exotoxin Z and pyrogenic exotoxin A.
AU Muller-Alouf, Heide; Proft, Thomas; Zollner, Thomas M.; Gerlach, Dieter; Champagne, Eric; Desreumaux, Pierre; Fitting, Catherine; Geoffroy-Fauvet, Christiane; Alouf, Joseph E.; Cavaillon, Jean-Marc (1)
CS (1) Department of Physiopathology, Institut Pasteur, 28 Rue Docteur Roux, 75015, Paris: jmcavail@pasteur.fr France
SO Infection and Immunity, (June, 2001) Vol. 69, No. 6, pp. 4141-4145. print. ISSN: 0019-9567.
DT Article
LA English

SL English
AB **Streptococcal** mitogenic exotoxin Z (**SMEZ**), a **superantigen** derived from **Streptococcus pyogenes**, provoked expansion of human lymphocytes expressing the Vbeta 2, 4, 7 and 8 motifs of T-cell receptor. **SMEZ** was pyrogenic in rabbits and stimulated the expression of the T-cell activation markers CD69 and cutaneous lymphocyte-associated antigen. A variety of cytokines was released by human mononuclear leukocytes stimulated with **SMEZ**, which was 10-fold more active than **streptococcal** pyrogenic exotoxin A. Th2-derived cytokines were elicited only by superantigens and not by **streptococcal** cells.

L11 ANSWER 4 OF 9 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

AN 2002:188931 BIOSIS

DN PREV200200188931

TI Molecular analysis of the immunological role of **streptococcal** mitogenic exotoxin Z.

AU Unnikrishnan, M. (1); Altmann, D. (1); Proft, T.; Fraser, J. D.; Cohen, J. (1); Sriskandan, S. (1)

CS (1) Imperial College School of Medicine, London UK

SO Abstracts of the General Meeting of the American Society for Microbiology, (2001) Vol. 101, pp. 280. <http://www.asmta.org/mtgsrsrc/generalmeeting.htm>. print.

Meeting Info.: 101st General Meeting of the American Society for Microbiology Orlando, FL, USA May 20-24, 2001
ISSN: 1060-2011.

DT Conference

LA English

AB **Streptococcal** mitogenic exotoxin Z is the most potent bacterial **superantigen** discovered to date. The biological function of **SMEZ** is unclear, but it may play a critical role in **streptococcal** pathogenesis; the gene is present in all strains studied and demonstrates extensive allelic variation. Aim: To characterize the immunological role of **SMEZ** in vitro and in vivo. Methods: **SmeZ** was insertionally inactivated in a clinical **Streptococcus pyogenes** strain, H293, to create strain H377. Proliferation of human PBMC, murine BALB/c, and HLA class II transgenic mouse splenocytes in response to purified r**SMEZ**, **SMEZ**+ and **SMEZ**-culture supernatants was measured by thymidine incorporation. Analysis of TCR Vbeta bearing T cell populations was performed by flow cytometry in human and murine cells. Mice were infected i.p. with either H293 or H377 and TCR Vbeta repertoire changes in spleen T cells were measured following infection. Results: Targeted disruption of **smeZ** was confirmed by Southern hybridisation and PCR. Despite the low level of expression of **SMEZ** in H293, disruption of **smeZ** led to a six-fold diminution of T cell proliferation in supernatant-stimulated human PBMC and a specific reduction in expansion of Vbeta8+ T cells. BALB/c mice splenocytes were poorly responsive to r**SMEZ** and did not proliferate in response to H293 or H377 supernatant. HLA-DQ transgenic murine spleen cells were highly responsive to r**SMEZ** compared with wild type and HLA-DR transgenic mice cells. HLA-DQ spleen cells were also highly responsive to H293 supernatant; proliferation was abolished by disruption of **smeZ** r**SMEZ** caused specific expansion of murine TCR Vbeta11+ (human TCR Vbeta8 gene homolog) T cells. In vivo experiments demonstrated expansion of mTCR Vbeta11 cells following infection with H293 in spleen; this expansion was significantly reduced in mice infected with H377 in the spleen, confirming that **SMEZ** can cause a **superantigen** effect in vivo, in invasive murine **streptococcal** sepsis. Conclusion: We clearly demonstrate the potency and TCR Vbeta-specific effects of **SMEZ**. Our results suggest a definite role for this **superantigen** in **streptococcal** pathogenesis.

L11 ANSWER 5 OF 9 WPIDS (C) 2003 THOMSON DERWENT DUPLICATE 3
AN 2000-452370 [39] WPIDS
DNC C2000-137919
TI Novel superantigens from **streptococcus** pyogenes useful for genotyping **streptococcus** pyogenes clones expressing **SMEZ-2** and for diagnosing a Kawasaki syndrome.
DC B04 D16
IN FRASER, J D; **PROFT, T**
PA (AUCK-N) AUCKLAND UNISERVICES LTD
CYC 91
PI WO 2000039159 A1 20000706 (200039)* EN 72p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL
OA PT SD SE SL SZ TZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES
FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS
LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL
TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2000019010 A 20000731 (200050)
EP 1141000 A1 20011010 (200167) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT
RO SE SI
JP 2002535966 W 20021029 (200274) 89p
ADT WO 2000039159 A1 WO 1999-NZ228 19991224; AU 2000019010 A AU 2000-19010 19991224; EP 1141000 A1 EP 1999-962603 19991224; WO 1999-NZ228 19991224; JP 2002535966 W WO 1999-NZ228 19991224; JP 2000-591070 19991224
FDT AU 2000019010 A Based on WO 200039159; EP 1141000 A1 Based on WO 200039159; JP 2002535966 W Based on WO 200039159
PRAI NZ 1998-333589 19981224
AB WO 200039159 A UPAB: 20000818
NOVELTY - A **superantigen** (I) **SMEZ-2**, SPE-G, SPE-H or SPE-J, or its functionally equivalent variant, is new.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:
(1) **SMEZ-2**, SPE-G, SPE-H, or SPE-J, having a 233, 234, 236, or 137 residue amino acid sequence, respectively, all fully defined in the specification;
(2) a polynucleotide (II) encoding (I), having a 702, 705, 711 or 414 nucleotide sequence, all fully defined in the specification, and encoding **SMEZ-2**, SPE-G, SPE-H, or SPE-J, respectively;
(3) a construct (III) comprising (I) and a cell-targeting molecule;
(4) a pharmaceutical composition comprising (III);
(5) an antibody (IV) which binds to (I);
(6) a nucleic acid molecule (V) which hybridizes to (II); and
(7) a kit which includes (II).
ACTIVITY - Cytostatic. No biological data given.
MECHANISM OF ACTION - T cell mitogens.
USE - (I) or (II) is used for subtyping **Streptococci** (claimed). They are also used for diagnosing a disease which is caused or mediated by expression of (I), in which the presence of (I) or (II) is detected by (IV) or (V), respectively, (claimed). The superantigens are used in diagnosis of disease such as Kawasaki syndrome. (II) can be used to design probes and primers for probing or amplifying parts of the **smez-2**, **spe-g**, **spe-h**, **spe-j** genes. They are also useful to recruit and activate T cells in a relatively non-specific fashion since they bind a large number of T cell receptor molecules by binding to the V beta domain. The constructs are useful in cancer therapy.
Dwg.0/13

L11 ANSWER 6 OF 9 BIOTECHDS COPYRIGHT 2003 THOMSON DERWENT AND ISI
AN 2000-12141 BIOTECHDS
TI Novel superantigens from **Streptococcus** sp. pyogenes useful for genotyping **Streptococcus** pyogenes clones expressing **SMEZ-2** and for diagnosing a Kawasaki syndrome;

recombinant **superantigen** production and DNA probe, DNA primer and antibody for Kawasaki syndrome and disease diagnosis and therapy

AU Fraser J D; Proft T
PA Auckland-Uniservices
LO Auckland, New Zealand.
PI WO 2000039159 6 Jul 2000
AI WO 1999-NZ228 24 Dec 1999
PRAI NZ 1998-333589 24 Dec 1998
DT Patent
LA English
OS WPI: 2000-452370 [39]
AB

A **Streptococcus pyogenes superantigen** (I) **SMEZ**-2, SPE-G, SPE-H or SPE-J, or its functionally equivalent variant, is claimed. Also claimed are: **SMEZ**-2, SPE-G, SPE-H or SPE-J, having a 233, 234, 236 or 137 amino acid protein sequence (specified), respectively; a DNA (II) encoding (I), having a 702, 705, 711 or 414 DNA sequence (specified), and encoding **SMEZ**-2, SPE-G, SPE-H or SPE-J, respectively; a construct (III) with (I) and a cell-targeting molecule; a pharmaceutical composition with (III); an antibody (IV) which binds to (I); a DNA probe (V) which hybridizes to (II); and a kit which has (II). (I) or (II) is used for subtyping **streptococci**. They are also used for diagnosing disease which is caused or mediated by expression of (I), in which the presence of (I) or (II) is detected by (IV) or (V), respectively. The superantigens are used in diagnosis of disease such as Kawasaki syndrome. (II) can be used to design DNA probes and DNA primers for probing or amplifying parts of the **smez**-2, spe-g, spe-h, spe-j genes. They are also useful to recruit and activate T-lymphocytes in a relatively non-specific manner. The constructs are useful in cancer therapy. (72pp)

L11 ANSWER 7 OF 9 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 4
AN 2000:293069 BIOSIS
DN PREV200000293069

TI The **streptococcal superantigen SMEZ** exhibits wide allelic variation, mosaic structure, and significant antigenic variation.

AU Proft, Thomas; Moffatt, S. Louise; Weller, Kylie D.; Paterson, A.; Martin, Diana; Fraser, John D. (1)
CS (1) Department of Molecular Medicine, School of Medicine, University of Auckland, Auckland New Zealand
SO Journal of Experimental Medicine, (May 15, 2000) Vol. 191, No. 10, pp. 1765-1776. print.
ISSN: 0022-1007.

DT Article
LA English
SL English

AB The frequencies of the newly identified **streptococcal superantigen** genes **smez**, spe-g, and spe-h were determined in a panel of 103 clinical isolates collected between 1976 and 1998 at various locations throughout New Zealand. **smez** and spe-g were found in every group A **Streptococcus** (GAS) isolate, suggesting a chromosomal location. The spe-h gene was found in only 24% of the GAS isolates and is probably located on a mobile DNA element. The **smez** gene displays extensive allelic variation and appears to be in linkage equilibrium with the M/emm type. 22 novel **smez** alleles were identified from 21 different M/emm types in addition to the already reported alleles **smez** and **smez**-2 with sequence identities between 94.5 and 99.9%. Three alleles are nonfunctional due to a single base pair deletion. The remaining 21 alleles encode distinct **SMEZ** variants. The mosaic structure of the **smez** gene suggests that this polymorphism has arisen from homologous recombination events rather than random point mutation. The recently resolved

SMEZ-2 crystal structure shows that the polymorphic residues are mainly surface exposed and scattered over the entire protein. The allelic variation did not affect either Vbeta specificity or potency, but did result in significant antigenic differences. Neutralizing antibody responses of individual human sera against different **SMEZ** variants varied significantly. 98% of sera completely neutralized **SMEZ-1**, but only 85% neutralized **SMEZ-2**, a very potent variant that has not yet been found in any New Zealand isolate. **SMEZ**-specific Vbeta8 activity was found in culture supernatants of 66% of the GAS isolates, indicating a potential base for the development of a **SMEZ** targeting vaccine.

L11 ANSWER 8 OF 9 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 5
AN 2000:375574 BIOSIS
DN PREV200000375574

TI Conservation and variation in **superantigen** structure and activity highlighted by the three-dimensional structures of two new superantigens from **Streptococcus pyogenes**.

AU Arcus, Vickery L.; **Proft, Thomas**; Sigrell, Jill A.; Baker, Heather M.; **Fraser, John D.**; Baker, Edward N. (1)

CS (1) School of Biological Sciences, University of Auckland, Auckland New Zealand

SO Journal of Molecular Biology, (26 May, 2000) Vol. 299, No. 1, pp. 157-168. print.

ISSN: 0022-2836.

DT Article

LA English

SL English

AB Bacterial superantigens (SAGs) are a structurally related group of protein toxins secreted by *Staphylococcus aureus* and **Streptococcus pyogenes**. They are implicated in a range of human pathologies associated with bacterial infection whose symptoms result from SAG-mediated stimulation of a large number (2-20%) of T-cells. At the molecular level, bacterial SAGs bind to major histocompatibility class II (MHC-II) molecules and disrupt the normal interaction between MHC-II and T-cell receptors (TCRs). We have determined high-resolution crystal structures of two newly identified **streptococcal** superantigens, SPE-H and **SMEZ-2**. Both structures conform to the generic bacterial **superantigen** folding pattern, comprising an OB-fold N-terminal domain and a beta-grasp C-terminal domain. SPE-H and **SMEZ-2** also display very similar zinc-binding sites on the outer concave surfaces of their C-terminal domains. Structural comparisons with other SAGs identify two structural sub-families. Sub-families are related by conserved core residues and demarcated by variable binding surfaces for MHC-II and TCR. **SMEZ-2** is most closely related to the **streptococcal** SAG SPE-C, and together they constitute one structural sub-family. In contrast, SPE-H appears to be a hybrid whose N-terminal domain is most closely related to the SEB sub-family and whose C-terminal domain is most closely related to the SPE-C/**SMEZ-2** sub-family. MHC-II binding for both SPE-H and **SMEZ-2** is mediated by the zinc ion at their C-terminal face, whereas the generic N-terminal domain MHC-II binding site found on many SAGs appears not to be present. Structural comparisons provide evidence for variations in TCR binding between SPE-H, **SMEZ-2** and other members of the SAG family; the extreme potency of **SMEZ-2** (active at 10-15 g ml⁻¹ levels) is likely to be related to its TCR binding properties. The **smz** gene shows allelic variation that maps onto a considerable proportion of the protein surface. This allelic variation, coupled with the varied binding modes of SAGs to MHC-II and TCR, highlights the pressure on SAGs to avoid host immune defences.

L11 ANSWER 9 OF 9 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 6
AN 1999:98436 BIOSIS

DN PREV199900098436
TI Identification and characterization of novel superantigens from
Streptococcus pyogenes.
AU Proft, Thomas ; Moffatt, S. Louise; Berkahn, Celia J.;
Fraser, John D. (1)
CS (1) Dep. Mol. Med., Sch. Med., Univ. Auckland, Private Bag 92019, Auckland
New Zealand
SO Journal of Experimental Medicine, (Jan. 4, 1999) Vol. 189, No. 1, pp.
89-101.
ISSN: 0022-1007.
DT Article
LA English
AB Three novel **streptococcal superantigen** genes (spe-g,
spe-h, and spe-j) were identified from the **Streptococcus**
pyogenes M1 genomic database at the University of Oklahoma. A fourth novel
gene (**smez-2**) was isolated from the *S. pyogenes* strain 2035,
based on sequence homology to the **streptococcal** mitogenic
exotoxin z (**smez**) gene. **SMEZ-2**, **SPE-G**, and **SPE-J** are
most closely related to **SMEZ** and **streptococcal**
pyrogenic exotoxin (**SPE**)-C, whereas **SPE-H** is most similar to the
staphylococcal toxins than to any other **streptococcal** toxin.
Recombinant (r)**SMEZ**, r**SMEZ-2**, r**SPE-G**, and r**SPE-H** were mitogenic
for human peripheral blood lymphocytes with half-maximal responses between
0.02 and 50 pg/ml (r**SMEZ-2** and r**SPE-H**, respectively). **SMEZ-2** is
the most potent **superantigen** (SAg) discovered thus far. All
toxins, except r**SPE-G**, were active on murine T cells, but with reduced
potency. Binding to a human B-lymphoblastoid line was shown to be zinc
dependent with high binding affinity of 15-65 nM. Evidence from modeled
protein structures and competitive binding experiments suggest that high
affinity binding of each toxin is to the major histocompatibility complex
class II beta chain. Competition for binding between toxins was varied and
revealed overlapping but discrete binding to subsets of class II molecules
in the hierarchical order (**SMEZ**, **SPE-C**) > **SMEZ-2** >
SPE-H > **SPE-G**. The most common targets for the novel SAgS were human
Vbeta2.1- and Vbeta4-expressing T cells. This might reflect a specific
role for this subset of Vbetas in the immune defense of gram-positive
bacteria.

WEST Search History

DATE: Monday, March 03, 2003

<u>Set Name</u>	<u>Query</u>	<u>Hit Count</u>	<u>Set Name</u>
side by side			result set
<i>DB=USPT,PGPB,JPAB,EPAB,DWPI,TDBD; PLUR=YES; OP=ADJ</i>			
L32	bacteria 5 adj superantigen	0	L32
L31	bacteria 5 adj earth	0	L31
L30	bacteria 5 adj earth	0	L30
L29	bacteri? 10Adj superantigen?	0	L29
L28	superantigen and Smez?2	1	L28
L27	proft-thomas.in.	0	L27
L26	proft-thomas.in.	0	L26
L25	fraser-john-d.in.	14	L25
L24	(bacteria 5 adj superantigen) AnD (((@pd > 20030227)!))	0	L24
L23	(bacteria 5 adj earth) AnD (((@pd > 20030227)!))	0	L23
L22	(bacteria 5 adj earth) AnD (((@pd > 20030227)!))	0	L22
L21	(bacteri? 10Adj superantigen?) AnD (((@pd > 20030227)!))	0	L21
L20	(superantigen and Smez?2) AnD (((@pd > 20030227)!))	0	L20
L19	(proft-thomas.in.) AnD (((@pd > 20030227)!))	0	L19
L18	bacteria 5 adj superantigen	0	L18
L17	(proft-thomas.in.) AnD (((@pd > 20030227)!))	0	L17
L16	bacteria 5 adj earth	0	L16
L15	(fraser-john-d.in.) AnD (((@pd > 20030227)!))	0	L15
L14	bacteria 5 adj earth	0	L14
L13	bacteri? 10Adj superantigen?	0	L13
L12	superantigen and Smez?2	1	L12
L11	bacteria 5 adj superantigen	0	L11
L10	proft-thomas.in.	0	L10
L9	bacteria 5 adj earth	0	L9
L8	proft-thomas.in.	0	L8
L7	fraser-john-d.in.	14	L7
L6	bacteria 5 adj earth	0	L6
L5	bacteri? 10Adj superantigen?	0	L5
L4	superantigen and Smez?2	1	L4
L3	proft-thomas.in.	0	L3
L2	proft-thomas.in.	0	L2
L1	fraser-john-d.in.	14	L1

END OF SEARCH HISTORY

*Streptococcal
mitogenic antigen 2*